ANTIMICROBIAL & ANTIMYCOBACTERIAL LECTURE OBJECTIVES:

1) Describe the general antibacterial spectrum and distribution pattern of each class of antimicrobials.

2) Describe the major route of excretion of each class of antimicrobials and how this may be beneficial or detrimental.

3) Discuss the adverse effects associated with each class of antimicrobials. Focus especially on those adverse effects that are the most serious and those that are the most frequent.

4) Describe the major drug interactions that are associated with each class of antimicrobials.

5) Certain antimicrobial agents are combined with another drug. Discuss the rationale for each of the drug combinations.

6) Recall which antimicrobials are contraindicated or to be avoided in pregnancy or during childhood.

Chemotherapeutics, Introduction

Ronald L. Mellgren, Ph.D.

Content:

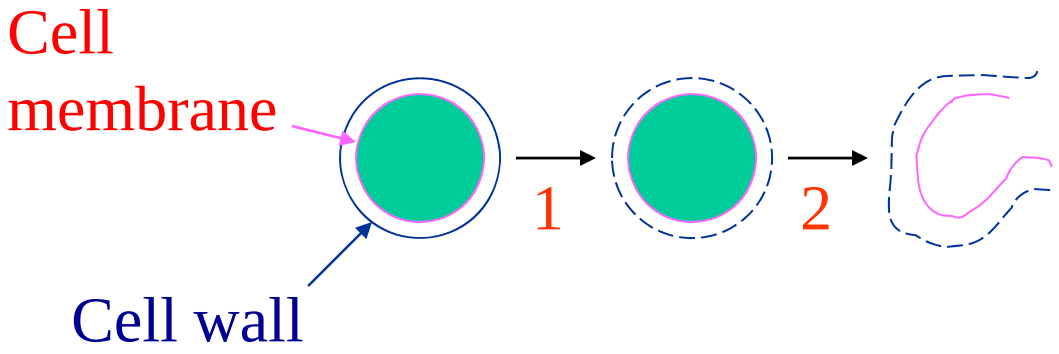
Mechanisms of selective toxicity

Basic concepts of chemotherapeutics

PRINCIPLES OF CHEMOTHERAPEUTICS

How do antimicrobials work? --- Selective toxicity

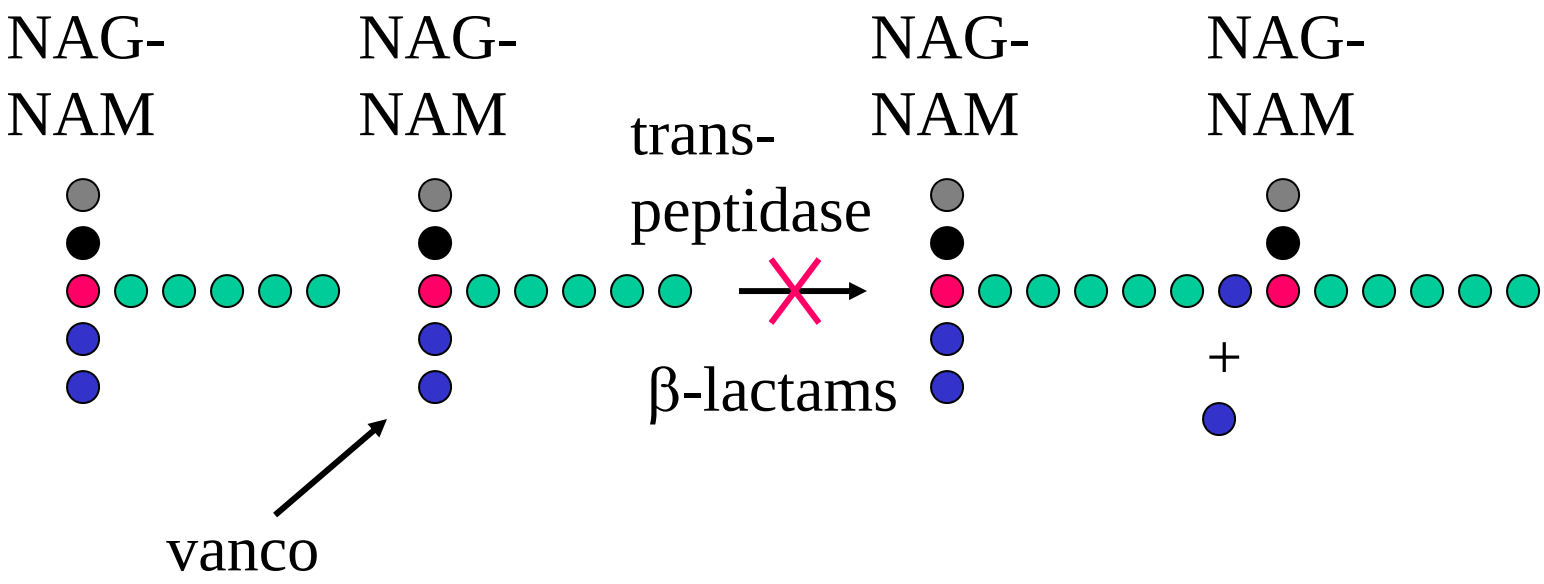
A. Inhibition of cell wall synthesis:



1 Examples: penicillins, cephalosporins, vancomycin
2 Cell lysis

Drugs that inhibit cell wall synthesis
are frequently bactericidal - they kill bacteria

MECHANISMS OF β-LACTAMS AND VANCOMYCIN



● = glycine
● = D-alanine

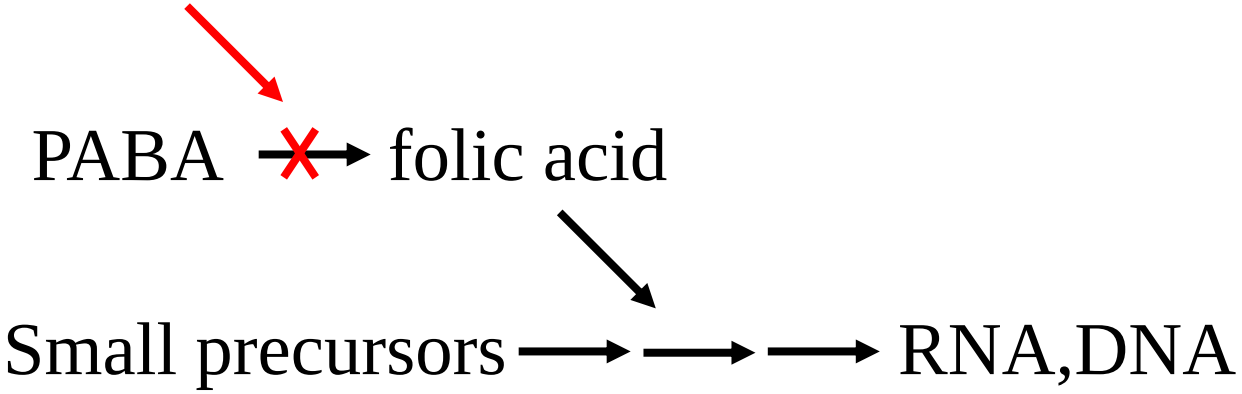
B. INHIBITION OF NUCLEIC ACID BIOSYNTHESIS:

Examples:

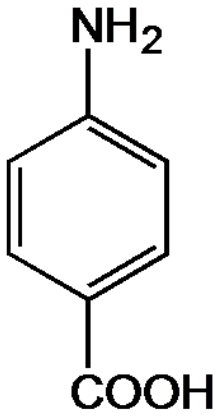
- Rifampin

Sulfonamides & other anti-metabolites are often bacteriostatic - they only slow growth

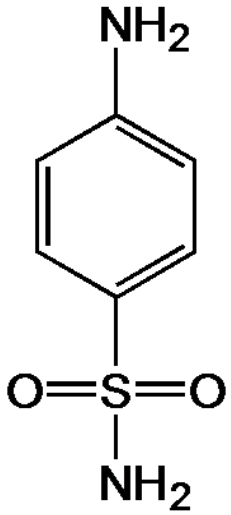
- Sulfonamides: ANTIMETABOLITES



ANTIMETABOLITES: drugs that mimic normal enzyme substrates and inhibit metabolism



PABA: para-amino benzoic acid

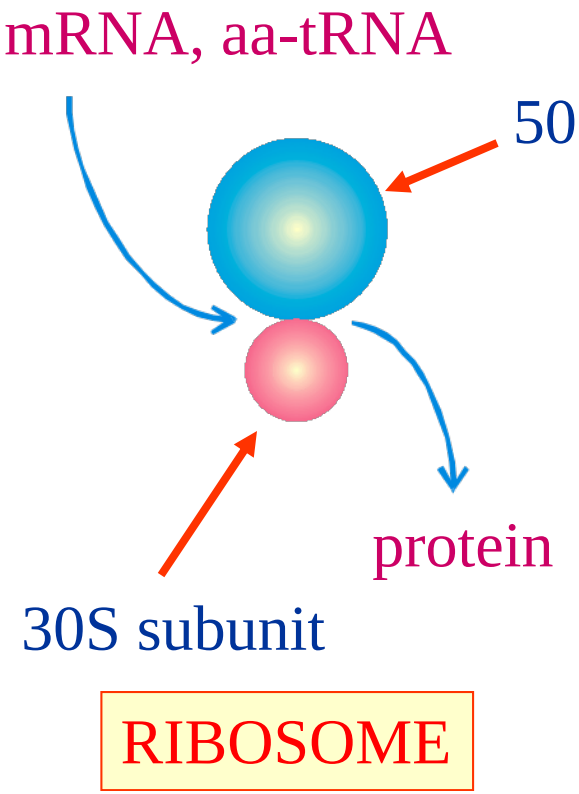


Sulfanylamide (a sulfonamide antimicrobial agent)

C. INHIBITION OF PROTEIN SYNTHESIS

Examples:

Tetracyclines, chloramphenicol, erythromycin



bacteriostatic

Aminoglycosides

bactericidal

FACTORS INFLUENCING DRUG CHOICE

- Sensitivity of the infecting organism to the drug
- Distribution of the drug within the body (will it get to the site of infection?)
- Relative toxicity of the drug
- Severity of the infection

DISTRIBUTION OF ANTIMICROBIALS

- For most sites, passive diffusion is the major route for drug uptake.
- However, some drugs may penetrate inflamed tissues and achieve therapeutic levels.
- Active transport of anionic and cationic drugs leads to their accumulation in the kidney, and their export from the brain.

OTHER FACTORS WHICH DETERMINE THE OUTCOME OF TREATMENT

- Condition of the infected tissue
  - dead tissue
  - abscess
  - kidney stones or other obstructions
- Status of the immune system
  - newborn and elderly
  - cancer or organ transplant patients
  - diabetic patients
  - AIDS patients
- Development of microbial resistance

SUPRAINFECTION

Definition: infection by another organism during treatment. Usually occurs in intestine, urogenital tract, or respiratory tract.

- Most likely to occur with use of BROAD SPECTRUM antibiotics
- Most likely to occur during PROLONGED treatment
- Most likely to occur in patients with IMPAIRED IMMUNE SYSTEM

USE OF DRUG COMBINATIONS

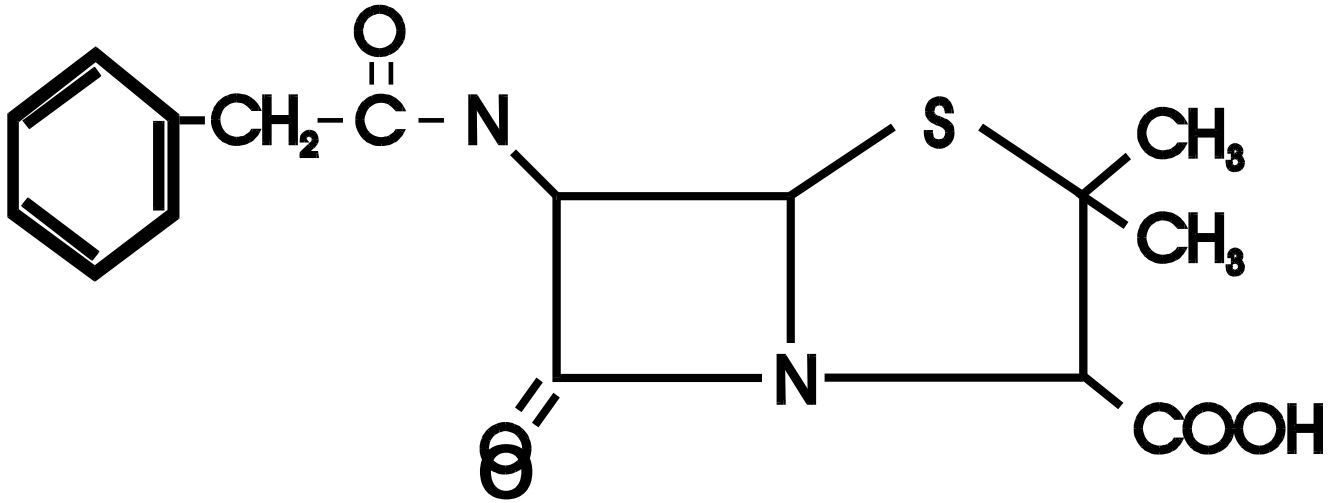
- Emergency treatment
- Prevention of resistance
- Synergism
- Mixed infections

Chemotherapeutics, The β-Lactam Antimicrobials

- Penicillins
- Cephalosporins
- Other β-lactams

THE β-LACTAM ANTIBIOTICS

Penicillin G (benzyl penicillin):



β-LACTAMS IN THE TOP 300 PRESCRIPTION DRUGS, 2008

Drug	Rank/300
Amoxicillin*	5
Cephalexin	28
Amoxicillin/clavulanate*	38
Cefdinir	100
Penicillin V	104
Cefuroxime axetil	239

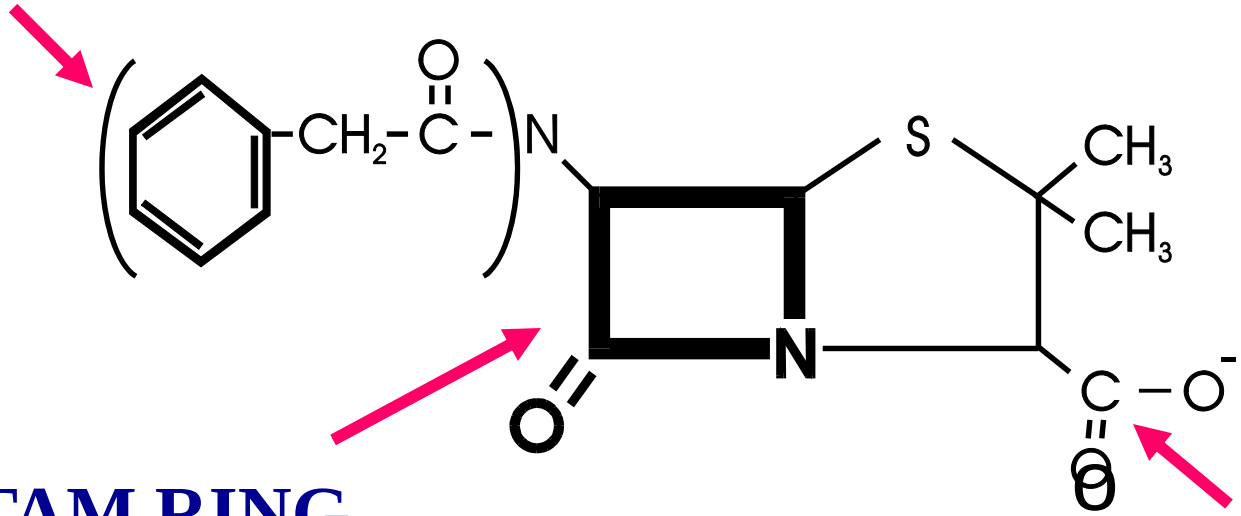
*__72,000,000__ prescriptions in total:
about one for every family/year in the USA

ANTIMICROBIAL SPECTRUM OF PENICILLIN G

ORGANISM	SENSITIVE	ORGANISM	SENSITIVE
Gram positive cocci		Gram negative bacilli	
Staph. aureus (now resistant)	(+)	*Bacteroides* Sp. (**except** *B. fragilis*)	+
Strep. pyogenes	+		
Strep. Pneumoniae (some resistant strains)	+	Nearly all others	-
Viridans *Strep.*	+	Other organisms	
Enterococcus faecalis	-	*Treponema pallidum*	+
Gram negative cocci		*Chlamidia* Sp.	-
Neisseria gonorrheae (many strains now resistant)	+		
Neisseria meningitidis	+		

STRUCTURE/FUNCTION RELATIONSHIPS IN PENICILLIN G:

"R" GROUP can be changed to alter antimicrobial properties



β–LACTAM RING

a. essential for antimic activity; target of bacterial β-lactamases

b. responsible for drug allergy

c. responsible for neurotoxicity

WEAK ACID GROUP

a. renal tubular secretion

b. potential cation toxicity

OVERCOMING PEN G's POOR PHARMACOKINETIC PROFILE

- Phenoxymethylpenicillin (Pen V) is acid stable, good oral availability.
- Repository penicillins:
  - Procaine Penicillin G
  - Benzathine Penicillin G
- Combination with probenicid decreases rate of renal secretion.

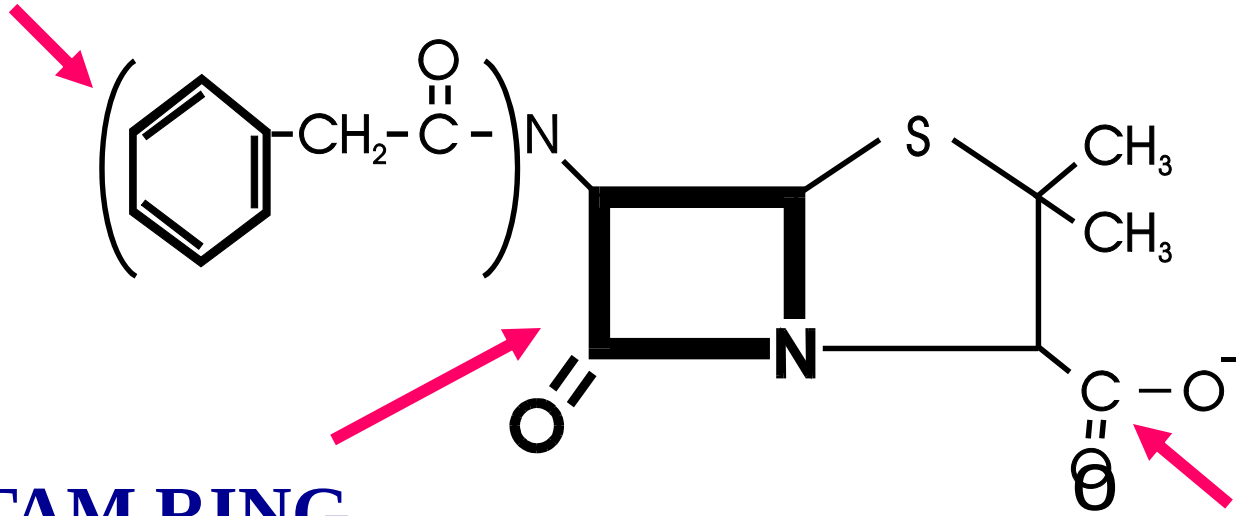
COMMENTS ON REPOSITORY PEN'S AND PEN V

- Repository pens are not soluble, and should **ONLY** be administered i.m.

- Pen V is useful for mild infections where its consistent absorption from the GI tract is important – However, it is less active than pen G *vs Neisseria*.

STRUCTURE/FUNCTION RELATIONSHIPS IN PENICILLIN G:

"R" GROUP can be changed to alter antimicrobial properties



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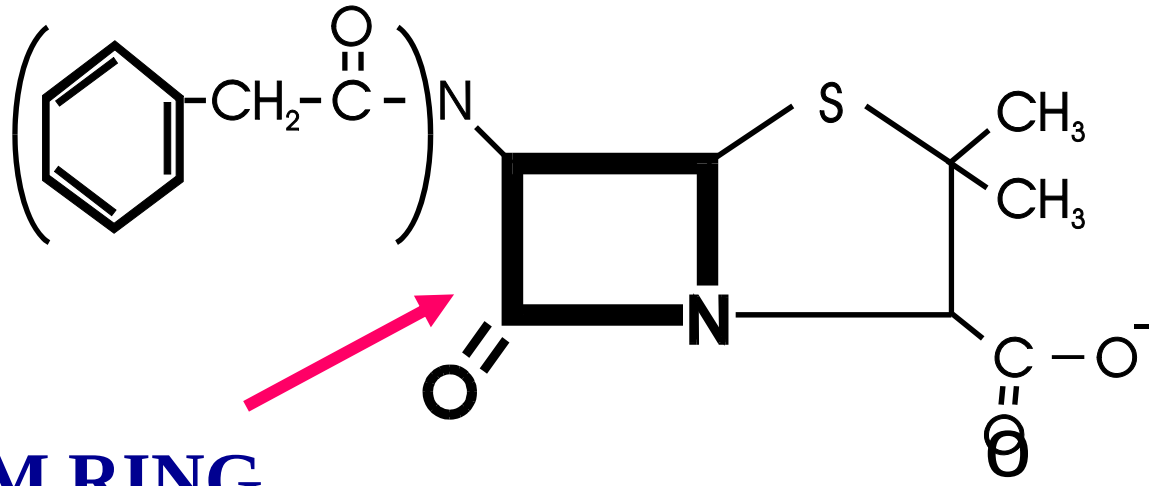

β–LACTAM RING

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Bacterial β-Lactamases

Ambler class:

A (serine penicillinases)

Specificity (example): pen (PC1); pen & ceph (TEM-1 to TEM-26); pen, ceph, & carbapenems (KPC-2)

B (metallo-β-lactamases)

Specificity (example): most β-lactams, including carbapenems (BcII)

C (cephalosporinases)

Specificity (example): cephalosporins (AmpC)

D (oxacillinases)

Specificity (example): penicillins, cloxacillin (Oxa-1)

Bacterial β-Lactamases

- Can be chromosomal, or plasmid borne.
  - Expression of chromosomal β-lactamases can be induced by β-lactams.
  - Plasmids bearing β-lactamases can be transmitted across bacterial species.
- Also classified on basis of specificity:
  - Penicillinases only hydrolyze β-lactam ring in penicillins
  - Can also have cephalosporinases and carbapenemases, that preferentially cleave these β-lactams.
  - Extended Spectrum β-Lactamases (ESBLs) cleave penicillins, cephalosporins, and sometimes also carbapenems (example = KPC-2)

β-LACTAMASE RESISTANT PENICILLINS

- Methicillin (no longer used)
- Oxacillin, Cloxacillin, Dicloxacillin
- Nafcillin

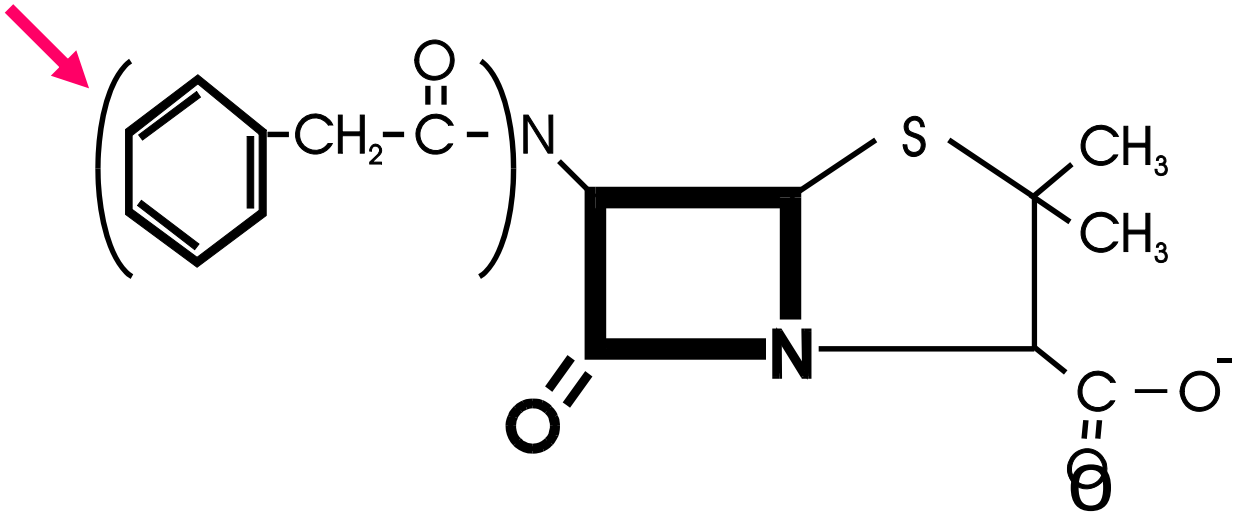
Use: Treatment of penicillin G-resistant *Staph. aureus*

COMMENTS ON THE PENICILLINASE-RESISTANT PENICILLINS

- Methicillin is no longer marketed because of renal toxicity (interstitial nephritis).
- Nafcillin is eliminated by biliary excretion – less chance of CNS toxicity in patients with compromised renal function.
- They are used exclusively against susceptible *Staph. aureus* strains. They are less active than other penicillins against most other organisms.

STRUCTURE/FUNCTION RELATIONSHIPS IN PENICILLIN G:

“R” GROUP can be changed to alter antimicrobial properties



BROAD SPECTRUM PENICILLINS

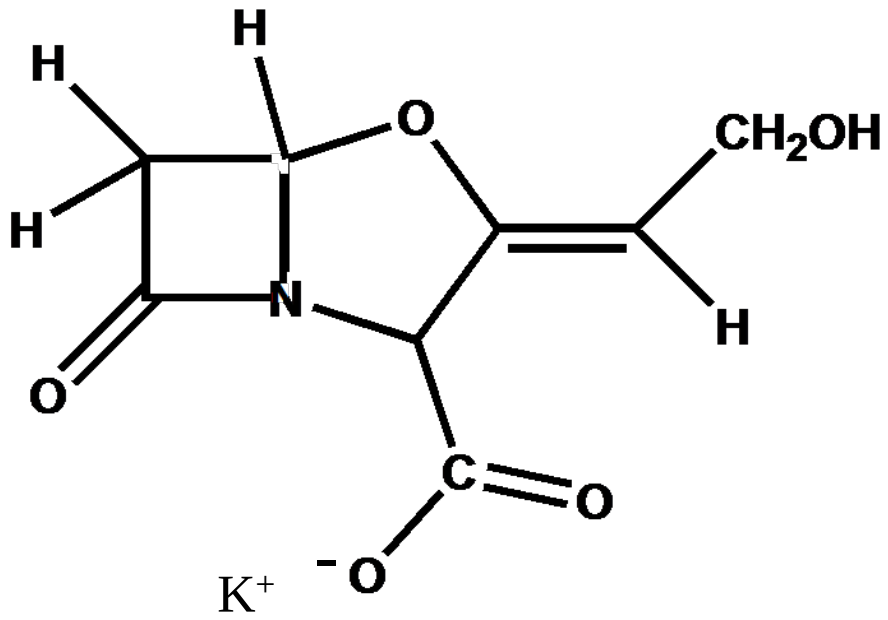
- Aminopenicillins: ampicillin, amoxicillin
  - These hit *E. coli*, *Proteus mirabilis*, salmonellae, and haemophilus species
- Carboxypenicillins: carbenicillin indanyl ester, ticarcillin
  - Extend spectrum to include *Pseudomonas*, indole-positive *Proteus*
- Ureidopenicillins: piperacillin, mezlocillin
  - Similar to ticarcillin, but also *Klebsiella pneumoniae*.

COMMENTS ON THE BROAD SPECTRUM PENICILLINS

- Amoxicillin *vs* ampicillin
  - Amoxicillin is better absorbed orally and causes less GI disturbance.
  - Ampicillin is available for both oral & parenteral use.
  - Antimicrobial spectrum is expanded and similar except: ampicillin has better activity than amoxicillin against shigella and listeria.
- Carbenicillin indanyl is concentrated in urine & only useful for UTIs.
- None of the broad-spectrum penicillins are resistant to β-lactamases.

ANOTHER APPROACH TO OVERCOMING β-LACTAMASES: INHIBITORS

Amoxicillin plus clavulanate (Augmentin®); Ampicillin plus sulbactam (Unasyn®); Ticarcillin plus clavulanate (Timentin®); Piperacillin plus tazobactam (Zosyn®)



Clavulanate: a β-lactamase inhibitor

β-LACTAM AND β-LACTAMASE INHIBITOR COMBINATIONS

- Serum half-lives and distribution profiles are similar.
- The lactamase inhibitor has negligible antimicrobial activity.
- The inhibitors block some plasmid-borne class A β-lactamases (found in *Staph.*, *H. influenzae*, *gonococcus*, *salmonella*, *shigella*, *E. coli* & *K. pneumoniae*).
- But many other β-lactamases are resistant, including chromosomal class C (*pseudomonas*, *enterobacter*, *citrobacter*, *serratia*).

Bacterial β-Lactamases

Inhibited by clavulanate

Ambler classes:

A (serine penicillinases)

Specificity (example): pen (**PC1**), pen & ceph (**TEM-1 to TEM-26**), pen, ceph, & carbapenems (KPC-2)

B (metallo-β-lactamases)

Specificity (example): most β-lactams, including carbapenems (BcII)

C (cephalosporinases)

Specificity (example): cephalosporins (AmpC)

D (oxacillinases)

Specificity (example): penicillins, cloxacillin (Oxa-1)

PENICILLIN ADVERSE EFFECTS

- Hypersensitivity – usually rash or serum sickness, BUT:
  - 1/10,000 patients have an immediate anaphylactic reaction
  - mortality = **10%**
- Neurotoxicity
  - Seizures or coma
  - associated with high doses of any penicillin (e.g., 60 g/day, *i.v.*)
- Cation toxicity – penicillins are administered as Na^+ or K^+ salts

PENICILLIN ADVERSE EFFECTS (continued)

- Fluid and electrolyte loss – high doses of any penicillin: penicillin anion is concentrated in renal tubules and produces an osmotic diuresis: increases Na^+ uptake by principal cells of collecting tubules & secretion of K^+ and H^+ into the luminal fluid. Thereby producing hypokalemic alkalosis.

- Herxheimer reaction: chills, fever, headache, muscle & joint pain shortly after first penicillin injection in patients with syphilis. Rash develops at syphilitic lesions – disappears in a few weeks. Does not recur with subsequent penicillin injections. Usually not necessary to withhold treatment.

PENICILLIN ADVERSE EFFECTS (continued)

- Coombs-positive hemolytic anemia
  - Penicillin dose > 6 grams/day
  - About 10% of patients will show a positive direct Coombs test.
  - A few patients will become anemic

- Interstitial nephritis

  Reason for withdrawal of methicillin from the market, but can be seen with other penicillins too at dosages >10 grams/day.

ADVERSE EFFECTS ASSOCIATED WITH SPECIFIC PENICILLINS

- Diarrhea, pseudomembranous colitis, maculopapular rash (the latter especially prevalent in patients with mononucleosis):

  Amoxicillin, ampicillin

- Prolonged bleeding:

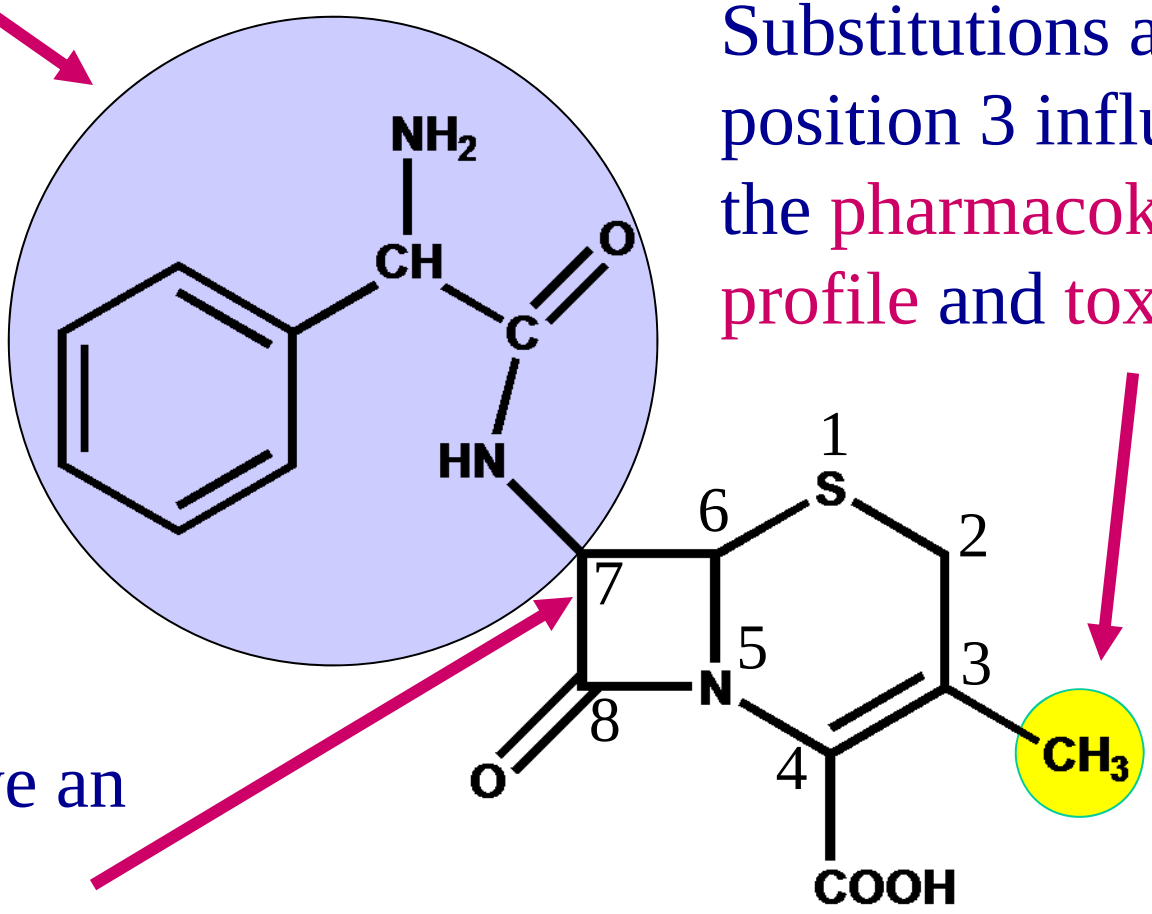
  Carbenicillin, ticarcillin

  -inhibit platelet aggregation

CEPHALOSPORINS

Substitutions at cephalosporin ring position 7 affect spectrum and stability to β-lactamases

Substitutions at ring position 3 influence the pharmacokinetic profile and toxicity



Cephamycins have an additional CH_3O- attached to ring position 7. They are even more resistant to β-lactamases

Cephalexin

CEPHALOSPORINS & PENICILLINS:

- Both are β-lactams
- Cephalosporins are resistant to cleavage by some β-lactamases (*e.g.*, *Staph*. β-lactamase)
- Cephalosporins have a broader antimicrobial spectrum than penicillin G. Useful for *K. pneumoniae* and *E. coli* infections.
- There is an approximately 10% incidence of cross-hypersensitivity between penicillins and cephalosporins: cephalosporins are generally too risky for use in patients who have had an anaphylactic episode with a penicillin.

THE THREE GENERATIONS OF CEPHALOSPORINS - AN OVERVIEW

- First and second generation cephalosporins are effective vs many Gm+ and Gm- organisms.
- Second generation are more active *vs* *Haemophilus* than 1st gen.
- Of the 1st and 2nd generation cephalosporins, only cefuroxime reaches CNS at therapeutic levels.
- Third generation cephalosporins have extended spectrum: active *vs* *Pseudomonas, Enterobacter, Serratia, Proteus*

THREE GENERATIONS OF CEPHALOSPORINS

	First Generation	Second Generation	Third Generation
Parenteral:	Cephalothin Cephapirin Cefazolin	Cefuroxime Cefotetan Cefoxitin Cefonicid Ceforanide Cefmetaxole	Cefotaxime Ceftizoxime Ceftazidime Ceftriaxone
Oral:	Cephradine Cephalexin (Keflex®) Cefadroxil	Cefaclor (Ceclor®) Loracarbef Cefprozil (Cefzil®) Cefuroxime-Axetil (Ceftin®) Cefpodoxime-proxetil	Cefixime Ceftibuten Cefdinir

Fourth Generation Cephalosporin: Cefepime (Maxipime®)

- Stable to hydrolysis by plasmid-encoded β-lactamases: TEM-1, TEM-2, and SHV-1
- Unlike other cephalosporins, **poor inducer** of chromosomal β-lactamases, and some extended-spectrum plasmid encoded β-lactamases. Also relatively resistant to most of these β-lactamases.
- NOT stable to some extended spectrum β-lactamases (e.g., TEM-3)

NOTABLE 1ST GENERATION CEPHALOSPORINS

- Cefazolin: a parenteral cephalosporin that is cleared by glomerular filtration and is highly protein bound. Consequently, it has a relatively long plasma half-life (~2hrs).
- Cephalexin: an orally administered drug that reaches sufficient plasma concentrations to inhibit many Gm^+ and Gm^- pathogens.

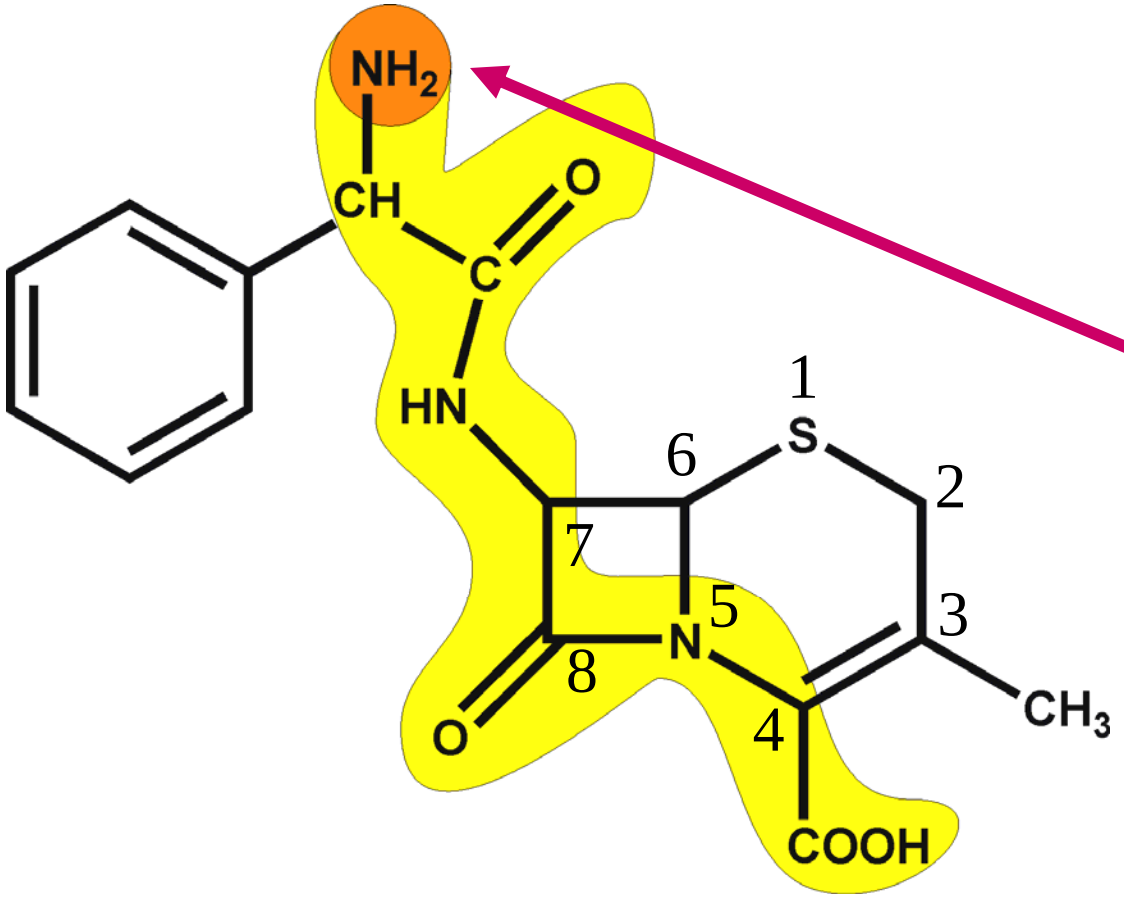
NOTABLE 2ND GENERATION CEPHALOSPORINS

- Cefoxitin and Cefotetan are both parenteral cephamycins with more activity than other 1st or 2nd generation cephalosporins against anaerobes, including *B. fragilis*.
- Cefprozil is an orally available cephalosporin with better activity against penicillin-sensitive *Strep.*, *E. coli*, *Proteus*, *Klebsiella*, and *Citrobacter* species than first generation cephalosporins.
- Cefuroxime axetil is an oral drug that has enhanced activity against *H. influenzae* and *M. catarrhalis* respiratory infections.

NOTABLE 3RD GENERATION CEPHALOSPORINS

- Ceftriaxone: drug of choice for treatment of gonorrhea. Also effective against many other Gm- pathogens. Cleared by biliary excretion; relatively long plasma $t_{1/2}$ (8 hours).
- Ceftazidime: best activity of all cephalosporins against *Pseudomonas* (plus aminoglycoside for pseudomonal meningitis).
- Cefdinir: oral drug used to treat respiratory tract infections caused by β-lactamase producing organisms.

GASTROINTESTINAL ABSORPTION OF CEPHALOSPORINS



Cephalexin

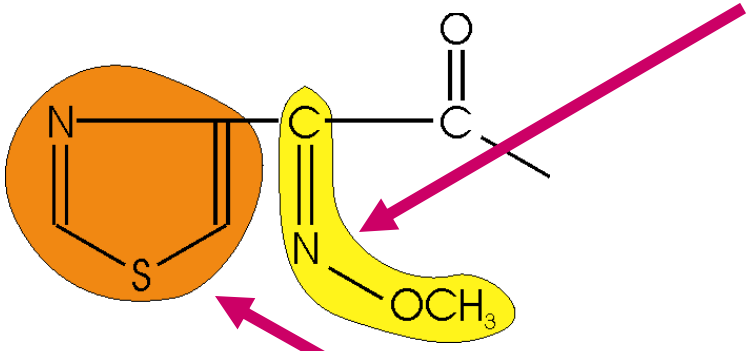
- Cephalosporins that can be administered orally have an alpha-amino group on the substituent attached to carbon 7.
- This structure allows uptake by a dipeptide transport system in the gut

SECOND GENERATION CEPHALOSPORIN SUBGROUPS

- Group A: increased activity against *H. influenzae*:
  - Cefuroxime
  - Cefamandol
  - Cefonicid
- Group B: increased activity against *B. fragilis*:
  - Cefoxitin
  - Cefotetan

THIRD GENERATION CEPHALOSPORINS

Aminothiazole oxime side chain on C7:



Present in:
Cefotaxime
Ceftizoxime
Ceftriaxone
-In Ceftazidime, the
-OCH_3 is replaced by a larger group

- Oxime ether group: stability to β-lactamases of enterobacteriaceae
  - Highly active against *E.coli*, *H. influenzae*, *K.pneumoniae*, *salmonella*, *shigella*, *P.mirabilis*
- Aminothiazole ring: affects binding to PBPs and entry into the periplasm

CEPHALOSPORIN ADVERSE EFFECTS

- The adverse effects associated with penicillins, are usually also observed with the cephalosporins.
- Kidney damage (direct tubular necrosis). Not observed yet with **Cephalexin**, Cefaclor, Cephradine, Cefadroxil, or Ceftizoxime.
- Adverse effects associated with the methythiotetrazole (MTT) cephalosporins (Cefamandole, Cefoperazone, **Cefotetan**)
  - **Delayed blood clotting** because of low prothrombin levels in blood
  - **Alcohol intolerance**

OTHER β-LACTAM ANTIMICROBIALS

- Carbapenems: meropenem & imipenem - cilastatin
  - Broad spectrum - **useful in emergency treatment**
  - No cross-resistance with other β-lactams: they are not recognized well by bacterial β-lactamases
- Aztreonam: Only effective against aerobic Gram neg. bacteria
  - Resistant to most β-lactamases
  - **Little cross-allergenicity** with other β-lactams

Imipenem-Cilastatin (Primaxin®)

- Cilastatin inhibits renal dehydropeptidase-1, an enzyme that inactivates imipenem.

- Cilastatin also helps prevent kidney toxicity of imipenem by blocking its active uptake and accumulation by renal tubule cells.

- CNS toxicity is the most serious adverse effect: decreased consciousness and myoclonic jerking. In part, this may result from cilastatin inhibition of imipenem transport out of the CSF.

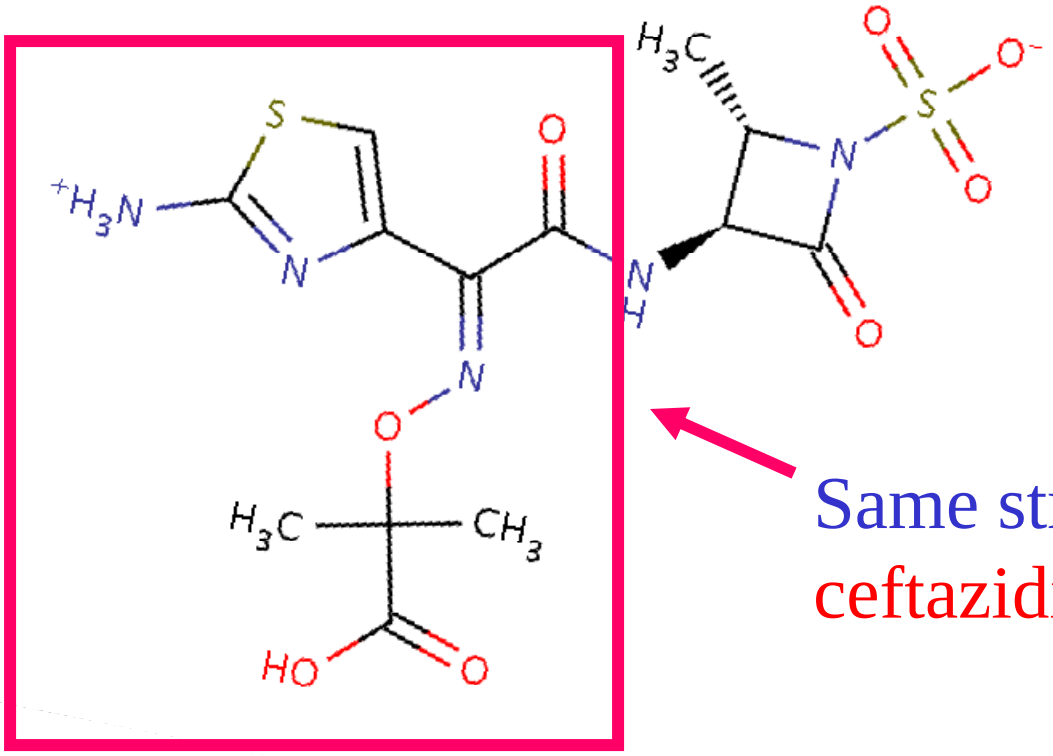
Meropenem (Merrem®)

- Antimicrobial spectrum is broad, like imipenem, somewhat less active *vs* Gm+ and more active *vs* Gm-
- Not hydrolyzed by dehydropeptidase-1
- Decreased incidence of CNS toxicity compared with imipenem/cilastatin
- Possibly increased renal toxicity

Aztreonam (Azactam®) A Monobactam

- Binds to PBP-3 which is ONLY present in aerobic Gram negative bacteria.
- Resistant to almost all β-lactamases, and does not induce expression of chromosomal β-lactamases.
- If chromosomal β-lactamases have been induced by other β-lactams, they will bind aztreonam and prevent it from binding to PBP-3.
- Little risk of cross-allergy with penicillins or cephalosporins (possible exception: ceftazidime).

Perez Pimiento, *et al*., *Allergy* **53**: 624 (1998): A patient developed hypersensitivity to aztreonam during treatment; subsequently shown to have allergic response to ceftazidime in both intradermal and skin patch tests.



AZTREONAM

Bacterial β-Lactamases

Ambler classes:

A (serine penicillinases)

Specificity (example): pen (PC1), pen & ceph (TEM-1 to TEM-26), pen, ceph, & carbapenems (KPC-2), ceph & aztreonam, (GES-13)

(Kotsakis, *et al*. *Antimicrob Agents Chemother* **54**: 1331, 2010)

B (metallo-β-lactamases)

Specificity (example): most β-lactams, including carbapenems (BcII)

C (cephalosporinases)

Specificity (example): cephalosporins (AmpC)

D (oxacillinases)

Specificity (example): penicillins, cloxacillin (Oxa-1)

ANTIMICROBIAL SPECTRUM OF PENICILLIN G

ORGANISM	SENSITIVE	ORGANISM	SENSITIVE
Gram positive cocci		Gram negative bacilli	
Staph. aureus (now resistant)	(+)	*Bacteroides* Sp. (**except** *B. fragilis*)	+
Strep. pyogenes	+		
Strep. Pneumoniae (some resistant strains)	+	Nearly all others	-
Viridans *Strep.*	+	Other organisms	
Enterococcus faecalis	-	*Treponema pallidum*	+
Gram negative cocci		*Chlamidia* Sp.	-
Neisseria gonorrheae (many strains now resistant)	+		
Neisseria meningitidis	+		

DRUGS USED AS β-LACTAM SUBSTITUTES

- Spectinomycin (Trobicin®)
  - Single i.m. injection for urethral gonorrhea
  - Low toxicity: nausea, chills, fever, dizziness

- Vancomycin (Vancocin®)
  - Treatment of meth.-resistant *Staph. aureus* (MRSA)
  - Backup drug for *C. difficile* pseudomembranous colitis.
  - Little activity *vs* Gm- bacilli

TOXICITY OF VANCOMYCIN (i.v. administration)

- Ototoxic: deafness, sometimes irreversible
- Nephrotoxic: Blood & protein in urine
- Thrombophlebitis: (clots in bloodstream) occur in over 10% of patients
- Hypotension & “red man” syndrome because the drug releases histamine. Administer antihistamines 2 hrs before infusing the drug slowly (over 1 hr) i.v.

NEW AGENTS PRIMARILY FOR β-LACTAM-RESISTANT Gm+ ORGANISMS

- Quinupristin/dalfopristin (Synercid®)
- Linezolid (Zyvox®)
- Daptomycin (Cubicin®)

Quinupristin/Dalfopristin (Synercid IV®)

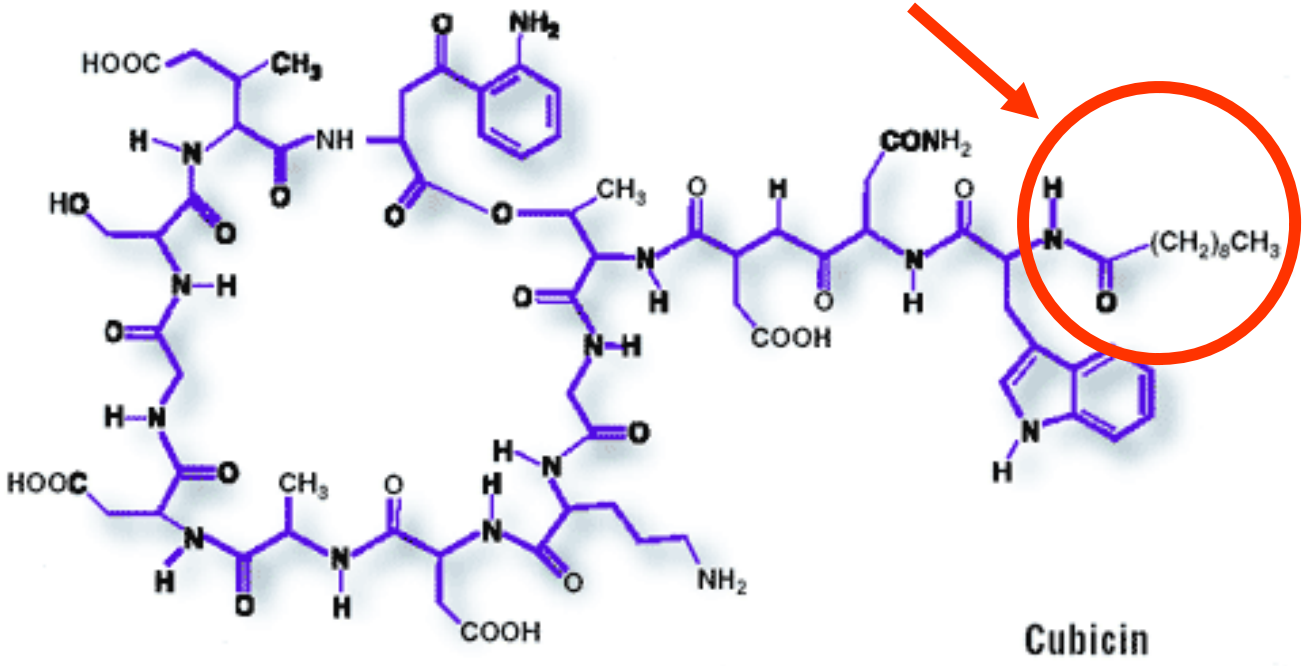
- A combination of two streptogramins: inhibitors of protein synthesis.
- Active against vancomycin-resistant and multidrug-resistant *Enterococcus faecium*.
- NOT active against *Enterococcus faecalis*.
- Main adverse reaction is muscle and joint pain
- Inhibits Cyp3A4.

Linezolid (Zyvox®)

- Parenteral and oral formulations for treatment of vancomycin-resistant enterococci.
- Also effective *vs* methicillin resistant *Staph. aureus* (MRSA).
- Binds to 23S ribosomal RNA – no cross-resistance with other protein synthesis inhibitors.
- Thrombocytopenia is possible. Platelet counts should be monitored if treatment exceeds two weeks.
- Linezolid inhibits monoamine oxidase (MAO) – patients should avoid foods rich in tyramine, or drugs metabolized by MAO.

Daptomycin (Cubicin®)

Decanoyl amide



- A cyclic lipopeptide antibiotic.
- Inserts in cell membrane and causes rapid depolarization.

Daptomycin (Cubicin®)

- Indicated for skin and skin structure infections caused by: *Staph. aureus* (including MRSA), *Strep. Pyogenes*, *Strep. Agalactiae*, *Strep. dysgalactiae* subsp. *equisimilis*, and *E. faecalis* (Vanco sensitive).
- Also indicated for *Staph. aureus* bacteremia and endocarditis.
- Toxicities:
  - Rhabdomyolysis: Monitor patients for muscle pain/weakness. Discontinue if blood CPK>1000 units/L. Consider temporary discontinuation of HMG-CoA reductase inhibitors ("statins").
  - Paresthesias (at high doses).

Chemotherapeutics: Inhibitors of Protein Synthesis

- Macrolides
- Clindamycin
- Tetracyclines
- Chloramphenicol
- Aminoglycosides

MACROLIDE ANTIBIOTICS: ERYTHROMYCIN

- Mechanism of action: binds to bacterial ribosomal 50S subunit, and inhibits peptidyl-tRNA translocation from the acceptor site to donor site.
- Mainly used for respiratory infections and urethral infections: effective against *Strep. pneumoniae*, *Strep. pyogenes*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*.
- Unstable in stomach acid. Usually given as drug ester, which is more stable: erythromycin ethylsuccinate or estolate.

ERYTHROMYCIN ADVERSE EFFECTS

- Most important adverse effect: **cholestatic hepatitis**, especially with the estolate ester. Incidence <1% of patients treated with erythromycin estolate. Most frequent in patients > 12 years old. Symptoms start about 2 weeks after initiation of therapy, and include severe abdominal pain, fever, pruritis. Reversible a few days after stopping treatment. Risk increases with pregnancy, and esters should be avoided.

ERYTHROMYCIN ADVERSE EFFECTS, CONTINUED

- Arrhythmias: prolongation of the QT interval, increasing the risk of potentially fatal torsades de pointes-type arrhythmia.
- Temporary hearing loss: associated with doses > 4 grams/day; impaired renal or hepatic function; age > 60 years.
- Gastrointestinal effects: erythromycin is a motilin agonist & stimulates migrating motor complex (MMC) activity – bands of intense contractile activity of intestinal smooth muscle.

MACROLIDES IN THE TOP 300 PRESCRIPTION DRUGS, 2008

Drug	Rank/200
Azithromycin	6
Clarithromycin	205

NEWER MACROLIDES: CLARITHROMYCIN AND AZITHROMYCIN

- About the same antimicrobial spectrum as erythromycin, but better tolerated because of fewer G.I. Effects. They also are less likely to produce the other adverse effects associated with erythromycin.
- Azithromycin is used to treat Chlamydial urethritis.
- Azithromycin and Clarithromycin are used to treat mycobacterial pneumonia (MAC pneumonia in AIDS patients).
- Drug interactions: Erythromycin and Clarithromycin inhibit cytochrome P_{450} drug metabolism. Azithromycin does so much less often.

CLINDAMYCIN

- Binds to 50S ribosomal subunit.
- Prophylaxis in dental procedures for patients with valvular heart disease.
- Severe infections outside the CNS caused by anaerobes including *Bacteroides fragilis* (MIC = 0.1 to 3 μg/ml).
- In combination with an aminoglycoside or cephalosporin for penetrating wounds of the abdomen or gut.
- Aspiration pneumonia

CLINDAMYCIN TOXICITY

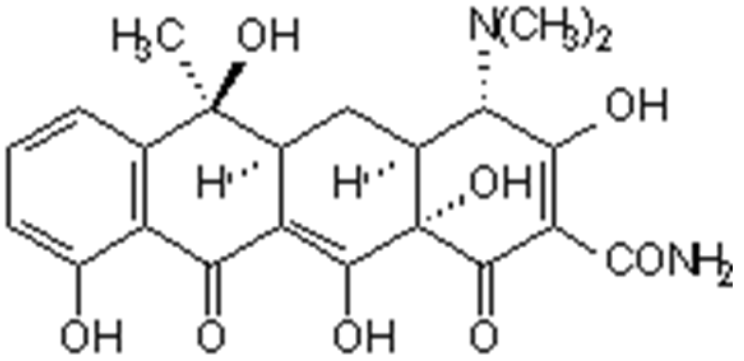
- Diarrhea, including **Pseudomembranous colitis in up to 10% of patients**. Treat with Metronidazole.
- Skin rashes, and rarely Stevens-Johnson syndrome.
- Hepatotoxicity is possible.

METRONIDAZOLE

- Active only against anaerobes: ferredoxin in sensitive bacteria chemically reduces metronidazole nitro group to produce toxic by-products.
- Well absorbed orally & well distributed
- Treatment of infections caused by *Clostridium difficile* and *Bacteroides fragilis*, and also the protozoa *Trichomonas vaginalis* and *Giardia lamblia*
- Toxicities: GI disturbances are the most common adverse effect, but also paresthesia, disulfiram reaction, ataxia/convulsions (rare). It is carcinogenic in rodents.

TETRACYCLINES

- Binds to 30S ribosomal subunit and inhibits tRNA binding
- Broad spectrum of activity against Gram pos. and Gram neg. bacteria
- Drugs of choice for only a few diseases:
  - Rickettsial infections like Rocky Mountain spotted fever
  - Cholera
  - Chlamydial infections
  - Acne



Tetracycline

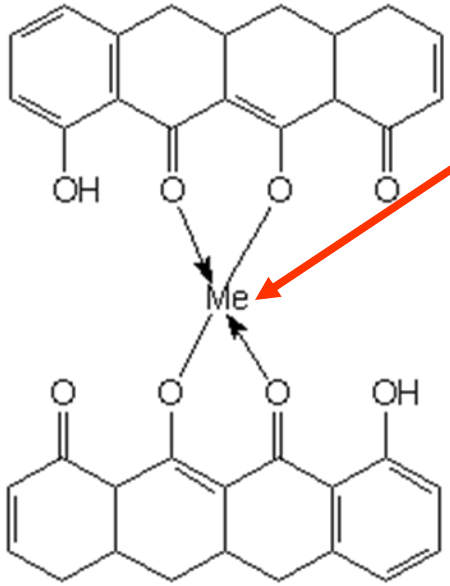
TETRACYCLINES IN THE TOP 300 PRESCRIPTION DRUGS, 2008

Drug	Rank/200
Doxycycline	68
Minocycline	182

TIGECYCLINE

- A glycylcycline derivative of minocycline
- Only administered intravenously
- Not exported by energy dependent drug efflux pump in most bacteria. Therefore active against bacteria that have developed resistance to other tetracyclines.
- Very broad spectrum. Active vs methicillin-resistant and vancomycin-resistant *Staph. aureus; enterococci*, including vanco-resistant; extended spectrum β-lactamase producing Gm- pathogens.

TETRACYCLINES CHELATE POLYVALENT METALS



Me = Ca^{2+}, Mg^{2+}, Fe^{2+}, Fe^{3+}, Al^{3+}….

DRUG	**CALCIUM BINDING (Tetracycline = 100)**
Chlortetracycline	130
Demeclocycline	190
Doxycycline	50

TETRACYCLINE TOXICITY

- Hepatotoxicity
  - >1-2 grams/day
  - **especially in pregnancy**
  - characterized by high blood bilirubin (jaundice)
  - **frequently fatal**
- Nephrotoxicity
  - Patients with renal disease. Doxycycline (Vibramycin®) may be safest to use.
  - Patients without history of renal disease: **Fanconi syndrome** from outdated tetracyclines
- Deposition in teeth and bones – fetus and children up to 8 years old.

TETRACYCLINE TOXICITY

- Gastrointestinal irritation with oral use: epigastric distress, nausea, diarrhea.

- Phototoxicity: esp. demethylchlortetracycline (Declomycin®) and doxycycline (Vibramycin®)

- Minocycline (Minocin®) can cause vertigo, ataxia, nausea & vomiting because of damage to the vestibule in the middle ear. Reversible upon discontinuing the drug.

TETRACYCLINE DRUG INTERACTIONS & CONTRAINDICATIONS

- Drug interactions:
  - Tetracyclines bind to calcium in dairy products, and calcium, magnesium or aluminum in antacids. This decreases absorption of the tetracycline.
  - Tetracycline & anticoagulant interaction: both interfere with clotting. Anticoagulant dose adjustment is required.
- Contraindications:
  - Pregnancy
  - Children 4 mo to 8 yrs old
  - Patients with renal impairment (Doxycycline is the possible exception).

CHLORAMPHENICOL

- Binds to 50S ribosome and prevents binding of amino acid part of aminoacyl-tRNA
- Used primarily as a backup drug:
- for β-lactams in treatment of *H. influenzae* or *N. meningitidis* meningitis in neonates and older children
- for tetracyclines
  - in pregnancy **except late stages**, see next slide
  - children 4 mo to 8 yrs old
  - renal insufficiency

CHLORAMPHENICOL TOXICITY

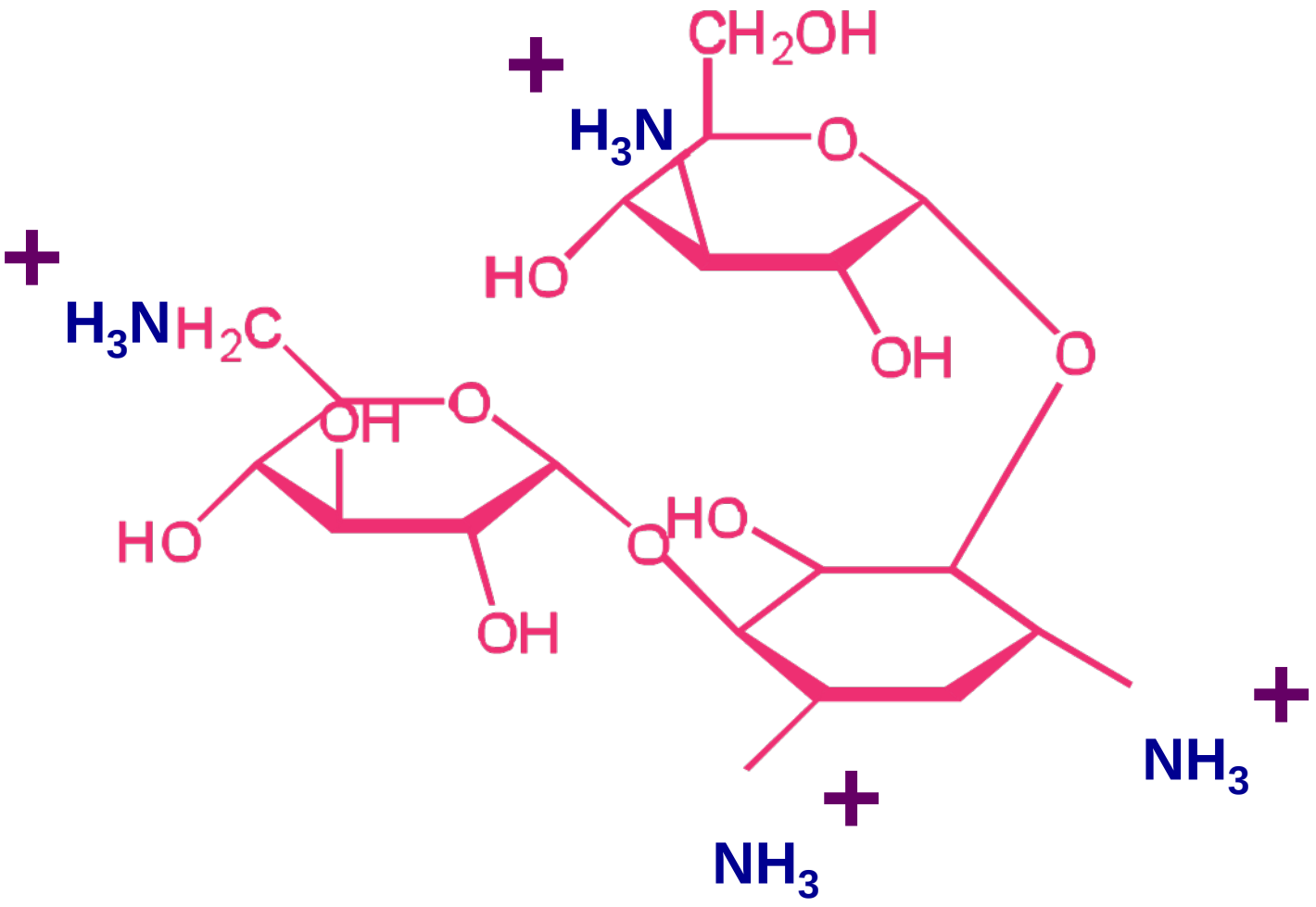
- Bone marrow depression, potential **aplastic anemia**. Occurs in 1/40,000 patients. Fatal.

- **Gray syndrome (gray baby syndrome)**. Respiratory depression produced by high blood levels of chloramphenicol. Can be fatal.

- Optic neuritis which may result in blindness.

- Diarrhea, pseudomembranous colitis (broad spectrum antibiotic).

AMINOGLYCOSIDES



AMINOGLYCOSIDES

- Binds to 30S ribosomal subunit and causes misreading of the genetic code.
- Bactericidal inhibitors of protein synthesis in aerobic, Gram-negative rods and some Gram-positive organisms.
- Must be administered parenterally for systemic infections: *i.v.* or *i.m.*, and tissue distribution is limited to extracellular space.
- Cleared by glomerular filtration.
- Resistance: impaired permeability or enzymatic inactivation: N-acetylation, O-phosphorylation, and O-adenylation.

AMINOGLYCOSIDES COMMONLY USED IN CLINICAL PRACTICE

- Streptomycin Predominantly used for treatment of pulmonary tuberculosis.
- Gentamicin (Garamycin®)
  - Aminoglycoside of first choice: cost, spectrum extended over streptomycin – hits Pseudomonas.
- Tobramycin (Nebcin®)
  - Somewhat enhanced anti-Pseudomonas activity compared with gentamicin

AMINOGLYCOSIDES COMMONLY USED IN CLINICAL PRACTICE: ENHANCED RESISTANCE TO INACTIVATING ENZYMES

- Amikacin (Amikin®)
  - Active against gentamicin and tobramycin-resistant organisms. It is only inactivated by bacterial N-acetyltransferase at the 6′ position on the aminoglycoside structure.
- Netilmicin (Netromycin®) Resistant to several of the bacterial enzymes that inactivate gentamicin and tobramycin.

TOXICITY OF THE AMINOGLYCOSIDES

- Nephrotoxicity: proximal tubular necrosis. Severe toxicity in ~2% of patients.
  - Usually reversible, but sometimes permanent
  - Increased BUN, decreased creatinine clearance, generally within a week or two of treatment
  - Aminoglycosides are cleared predominantly by glomerular filtration (they are poorly protein-bound, and thus readily filtered).
  - Concurrent administration of loop diuretics (ethacrynic acid, bumetanide, furosemide) will potentiate renal toxicity of the aminoglycosides.

OTOTOXICITY OF AMINOGLYCOSIDES

- Can be permanent
- Aminoglycosides accumulate in the perilymph
- Vestibular damage: difficulty with balance & walking, dizziness
- Cochlear: high-pitched ringing in the ears (tinnitus)
- Vestibular damage may only appear several weeks after termination of treatment.
- As with nephrotoxicity, ototoxicity is exacerbated by the loop diuretics.

AG TOXICITY (Continued)

- The therapeutic index of all currently available aminoglycosides is poor. MICs for sensitive organisms are frequently 1 μg/ml or higher, and toxicity is frequently observed at serum trough levels >2 μg/ml for > a few days.
- Fortunately, aminoglycosides have a post-antibiotic effect – they continue to slow microbial growth for several hours after the blood levels decrease below the MIC. Allows once-daily dosing.
- Therapeutic goal: peak serum levels 5-10 μg/ml; trough levels below 2 μg/ml.

OTHER TOXICITIES OF THE AMINOGLYCOSIDES

- Neuromuscular junction blockade
  - Observed with overdosage of aminoglycosides
  - Reversed by neostigmine
  - Use caution when simultaneously employing neuromuscular blocking drugs.
- Hypersensitivity
- Suprainfection

NITROFURANTOIN (Macrodantin®, Furadantin®)

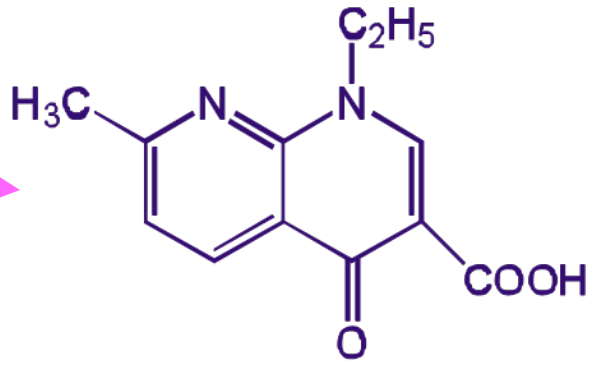
- Rapidly accumulates in the urinary tract, and does not reach therapeutic levels elsewhere.
- Sterilizes the urine
- Little tendency to produce resistant strains of enteric bacteria.
- Contraindicated in patients with renal functional impairment: under these conditions nitrofurantoin will accumulate in tissues, but will not reach adequate levels in urine.

Chemotherapeutics: Drugs Affecting Nucleic Acids

- Quinolones
- Sulfonamides

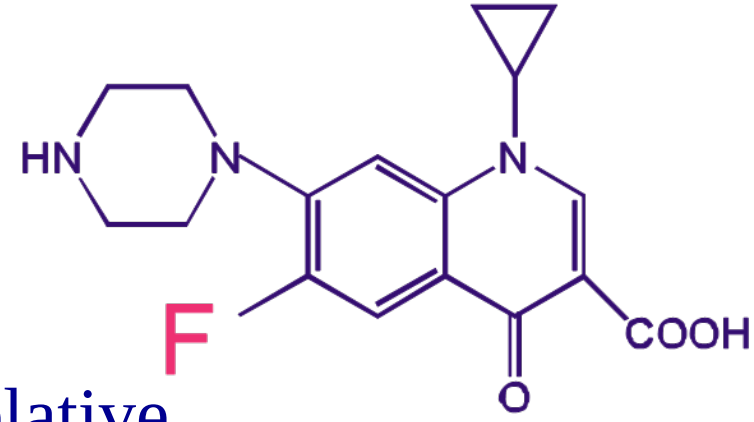
QUINOLONES AND FLUOROQUINOLONES

Nalidixic acid



a quinolone used for treatment of urinary tract infections. Spectrum: *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus spp.*

Ciprofloxacin



a fluoroquinolone useful for treatment of many systemic infections. Broad spectrum relative to nalidixic acid

FLUOROQUINOLONES IN THE TOP 300 PRESCRIPTION DRUGS, 2008

Drug	Rank/200
Ciprofloxacin	34
Levofloxacin	64
Moxifloxacin	184

FLUOROQUINOLONES

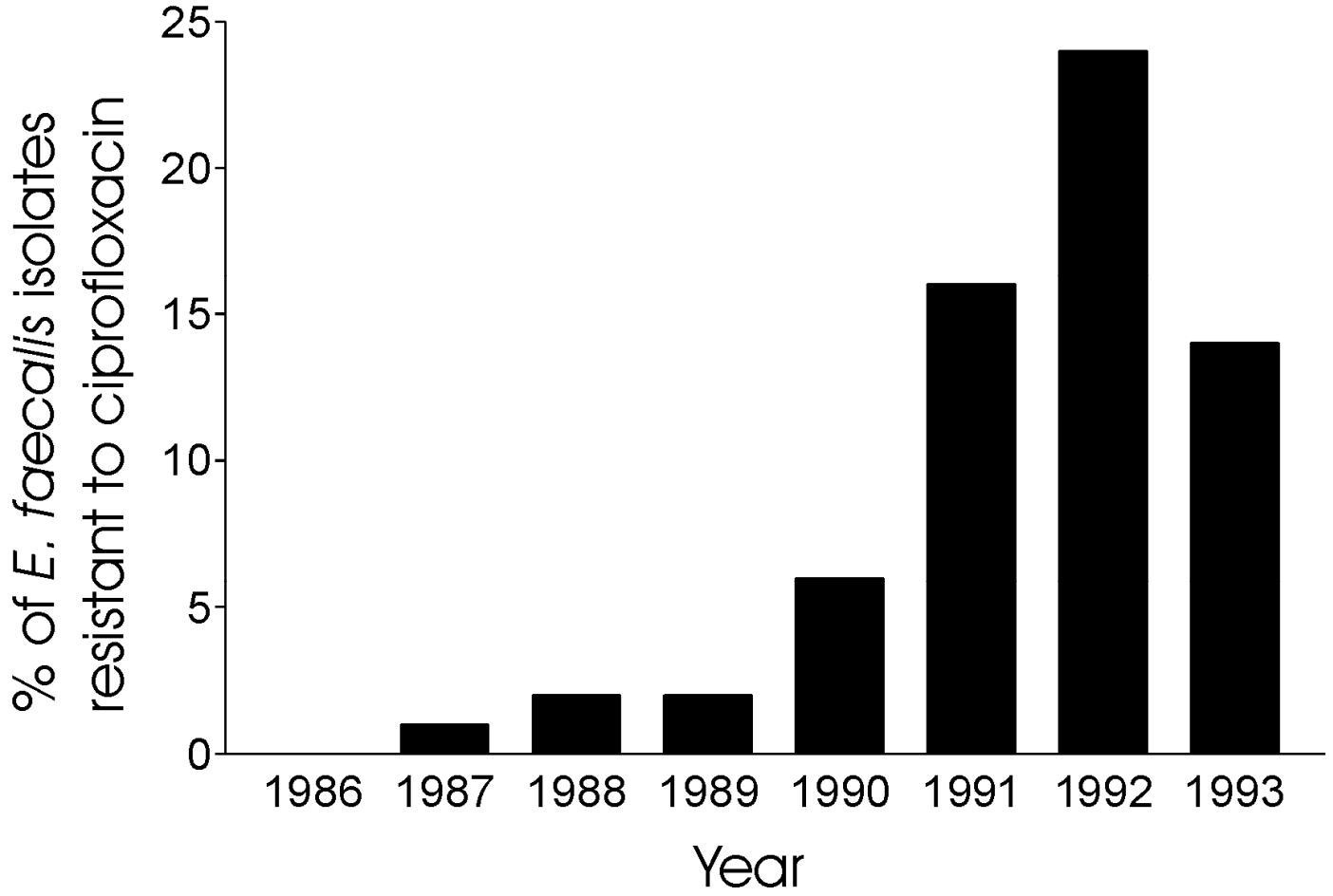
- Inhibitors of bacterial DNA gyrases
- Exceptionally broad spectrum - rapidly bactericidal against many Gm+ and Gm- bacteria.
- Resistance develops rapidly.
  - Resistance to one fluoroquinolone usually means resistance to all of them.
  - *M. tuberculosis*: the MfpA protein mimics DNA
- In general, anaerobes are intrinsically resistant.
  - Moxifloxacin will hit anaerobes.

CLINICAL USES OF THE FLUOROQUINOLONES

- Urinary tract infections
- Diarrhea caused by Campylobacter, *E. coli*, Salmonella, or Shigella
- Gonococcal infections (ciprofloxacin, ofloxacin)
- Prophylaxis of anthrax (ciprofloxacin, levofloxacin)
- Respiratory tract infections
  - Gm-: ciprofloxacin or levofloxacin
  - Anaerobes or pneumococcus: gatifloxacin, moxifloxacin, and levofloxacin

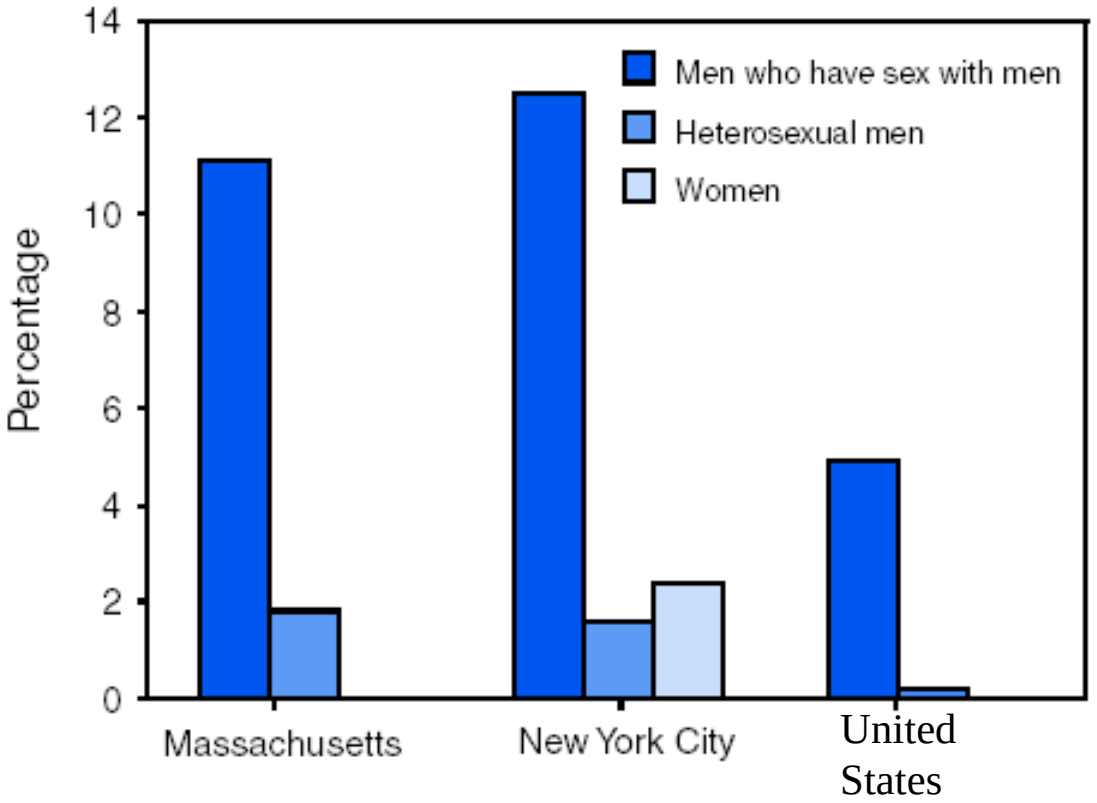
DEVELOPMENT OF RESISTANCE TO CIPROFLOXACIN: 1986-1993

(data from Tankovic, *et al*., Antimicrob. Agents Chemother. **40**: 2558, 1996)



INCREASED RESISTANCE TO FLUOROQUINO-LONES IN GONORRHEA

FIGURE. Prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infection, by sex, sexual behavior, and surveillance site — United States, 2003*



"In the absence of antimicrobial susceptibility testing or tests of cure, fluoroquinolones should no longer be used to treat proven or suspected gonococcal infections in MSM in the United States." -Morbidity and Mortality Weekly Report, 53: 335, 2003.

ADVERSE EFFECTS OF THE FLUOROQUINOLONES

- Cartilage erosion: not recommended for children (except perhaps in treatment of cystic fibrosis), or for pregnant or nursing women.
- Seizures: caused by binding to γ-aminobutyric acid (GABA) receptors.
- Photosensitivity – patients should avoid sunlight
- Cardiac effects: Fluoroquinolones prolong the QTc interval, increasing the risk of ventricular tachy-arrhythmias
- Pseudomembranous colitis

ADVERSE EFFECTS OF THE FLUOROQUINOLONES

- Achilles tendinitis and possible rupture: fluoroquinolones should be discontinued at the first sign of tendon pain or inflammation. Patients should not exercise until tendinitis has been ruled out.
- Hepatotoxicity: Trovafloxicin (Trovan®) has been linked with 14 cases of liver failure.
- Hypoglycemia in elderly diabetics. Hyperglycemia in non-diabetics; especially with gatifloxacin (Tequin®), which is contraindicated in diabetes mellitus.
- Allergic reactions in 0.5 - 2% of patients (rashes & itching)

FLUOROQUINOLONE DRUG INTERACTIONS

- Antacids containing Ca^{2+}, Mg^{2+}, Zn^{2+}, Bi^{2+}, or Al^{3+} may reduce the oral bioavailability of fluoroquinolones.
- Fluoroquinolones may increase the anticoagulant effect of warfarin.
- Fluoroquinolones may increase the plasma concentration of theophylline.

ANTIBACTERIAL SULFONAMIDES

- Once mainstays of antimicrobial therapy, but now mainly used in combination with dihydrofolate reductase inhibitors (e.g. trimethoprim) for susceptible organisms.
- Adverse effects:
  - Hypersensitivity
  - Blood disorders
  - Crystalluria
  - Jaundice and kernicterus of the newborn

TRIMETHOPRIM & SULFAMETHOXAZOLE (Bactrim^{R})

- Sulfamethoxazole is a sulfonamide
- Trimethoprim inhibits bacterial dihydrofolate reductase